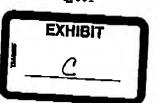
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October 4, 2001

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PLEASE DELIVER TO:	PHONE NO.	FAX No.
John Bonfiglio	(858) 799-9103	(858) 452-1222
Cypress Bioscience Inc.		(000) 402-1222

FROM:

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NUMBER OF PAGES, INCLUDING COVER: 7	CLIENT NUMBER: 093330-2108
LORIGINALS TO FOLLOW, No.	REQUESTOR#: 11357

RE: DRAFT U.S. PATENT APPLICATION METHODS OF TREATING PAIN

OUR REF: CYPR-023/00US

MESSAGE:

Enclosed are draft claims and an outline for the above-referenced patent application. If you have any questions, please feel free to contact me at the above number, or Ann Pease or (650) 843-5222.

585215 v1/PA CJJZ011.DOC

> If you do not receive all of the pages, please call ANIE K. ROCHE at (650) 843-5703 as soon as possible.

NO. 3176

3. SUMMARY OF THE INVENTION

This section will describe the various inventions that will be disclosed and claimed, and will include at least the following:

- Method to treat FMS
 - SNRI, which inhibits NE reuptake greater than serotonin reuptake [[Need to carve out tricyclics. Amitriptyline (1:1.6) and nortriptyline (1:168). Probably do not need to carve out dothiepin as 1:1 ratio. What is the ratio for doxepin and cyclobenzappine? Any other tricylics that need to be carved out?]]
 - Sustained release formulation
- Method to treat pain
- BRIEF DESCRIPTION OF THE FIGURES 4.
- DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS 5.
 - 5.1 Abbreviations

5.2 **Definitions**

- Dual serotonin norepinephrine reuptake inhibitor—greater inhibition of norepinephrine than serotonin reuptake. Carve out certain tricyclics.
- Therapeutically effective amount
- Adjunctively administered:
 - > Covers simultaneous administration (with same pill)
 - > Simultaneous administration with two separate pills

> Administration of one, followed by later separate administration of the other

5.3 SNRIs for treating Pain and Fibromyalgia

- Suggestion in art that greater norepinephrine activity increases analgesia
- But, see WO 01/26623
 - Even though noradrenergic pathways play a role in pain transmission, norepinephrine reuptake inhibitors like tricyclics had to be used in combination with phenylalanine or tyrosine to be effective.
- Present invention is directed to use of SNRIs which inhibit norepinephrine reuptake greater than serotonin reuptake for pain and fibromyalgia.
 - Contrary to the information in the art, administration of SNRIs which inhibit norepinephrine reuptake greater than serotonin reuptake, in the absence of phenylalanine or tyrosine, are effective for treatment of pain and fibromyalgia.

5.4 Sustained release formulations

Include information from the French application.

5.5 Dosages

This section will describe the various doses that can be used.

6. **EXAMPLES**

This section will describe a prophetic clinical trial on use of milnacipran to treat fibromyalgia.



What is claimed is:

- A method of treating fibromyalgia and/or associated symptoms of pain in an 1. animal subject, comprising administering to the animal subject, in need thereof, a therapeutically effective amount of a dual serotonin norepinephrine reuptake inhibitor compound, wherein said dual scrotonin norepinephrine reuptake inhibitor compound is characterized by a greater inhibition of norepinephrine reuptake than serotonin reuptake, and wherein said compound is not administered adjunctively with phenylalanine or tyrosine.
- The method according to claim 1, wherein the ratio of inhibition of serotonin 2. reuptake to norepinephrine reuptake by the compound is in the range of from about 0.5-1:2-30.
- The method according to claim I, wherein the compound is milnacipran [[Any 3. other compounds?]] Shuto?
 - 4. The method according to claim 1, wherein fibromyalgia is treated.
- The method according to claim 1, wherein associated symptoms of pain are 5. treated.
- The method according to claim 1, wherein the compound is adjunctively 6. administered with [[Are there any compounds that could be coadministered with milnacipran, for example to provide synergistic effects.]]
 - The method according to claim 1, wherein the animal subject is a human. 7.
- The method according to claim 1, wherein the therapentically effective amount 8. is from [[Need dosage ranges]] 12.5 -> 200mg/day
- 9. The method according to claim 1, wherein the compound is a NMDA receptor antagonist.
- The method according to claim 1, wherein the compound is formulated in a 10. sustained release dosage formulation.

NO. 3176

- A method of treating pain in an animal subject, comprising administering to the 11. animal subject, in need thereof, a therapeutically effective amount of a dual serotonin norepinephrine reuptake inhibitor compound, wherein said dual serotonin norepinephrine reuptake inhibitor compound is characterized by a greater inhibition of norepinephrine reuptake than serotonin reuptake, and wherein said compound is not administered adjunctively with phenylalanine or tyrosine.
- The method according to claim 11, wherein the ratio of inhibition of serotonin 12. reuptake to norepinephrine reuptake by the compound is in the range of from about 0.5-1:2-30.
 - The method according to claim 11, wherein the compound is milnacipran. 13.
- The method according to claim 11, wherein the compound is adjunctively 14. administered with [[Are there any compounds that could be coadministered with milnacipran, for example to provide synergistic effects.]]
 - The method according to claim 11, wherein the animal subject is a human. 15.
- The method according to claim 11, wherein the therapeutically effective amount 16. is from [[Need dosage ranges]]
- The method according to claim 11, wherein the compound is a NMDA receptor 17. antagonist.
- The method according to claim 11, wherein the compound is formulated in a 18. sustained release dosage formulation.